Are Children Suffering From Congenital Pseudarthrosis of the Tibia Associated With Bone Quality Decreased?

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Research

Keywords: congenital pseudarthrosis of the tibia, bone quality, quantitative ultrasound

Posted Date: August 17th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-806087/v1>

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Abstract

Background: Congenital pseudarthrosis of the tibia (CPT) is a rare and difficult to treat congenital disease in neonates. Our team's previous study found that exosomes derived from serum of children with CPT can reduce the effect of bone formation. In this study, we used ultrasound bone densitometry to detect the bone quality between children with CPT and those non-metabolic disease children, to determine the bone strength of children with CPT.

Methods: A total of 37 CPT children and 40 children without the bone metabolic disease (control group) were recruited in our hospital. The ultrasonic bone densitometer was used to examine the bilateral calcaneus of the subjects. According to the measurement results, we collected the broadband ultrasonic attenuation (BUA), sound transmission velocity (SOS), quantitative ultrasound index (QUI), bone strength index (STI) and bone mineral density estimation (BMD_e) values. For the intergroup analysis, t test was used to determine the differences of various quantitative measurements. Multivariable regression was used to examine the associations between quantitative ultrasound measurements differences and age, body mass index (BMI), neurofibromatosis type 1 (NF1) and CPT Crawford type. Intra-class correlation coefficient (ICC) was calculated to estimate intra- and inter-rater agreements.

Results: Seventy-four calcaneus scans from CPT patients (23 boys and 14 girls) and 80 calcaneus scans (24 boys and 16 girls) from the control. The CPT patients exhibited significantly lower SOS (1368.75 ± 136.78 m/s), STI (7.2319 ± 38.6525), QUI (8.2532 ± 56.1720) and BMD_e (-0.0241 ± 0.3552 g/cm³) than the control (SOS: 1416.02 ± 66.15 m/s, STI: 7.96 ± 16.884 , QUI: 28.8299 ± 25.461 , BMD_e: 0.0180 ± 0.1610 g/cm³). Multiple linear regression revealed that SOS, STI, QUI was statistically significant and negatively correlated with CPT Crawford classification.

Conclusions: We found the incidence of decreased bone quality in CPT group was higher than that in the non-bone metabolic disease group. This phenomenon was not related to NF1 while related to CPT Crawford classification, which suggested that the higher grade of the CPT Crawford classification, the lower the bone strength and the higher the risk of fracture.

Introduction

Congenital pseudarthrosis of the tibia (CPT) is rare and difficult to treat congenital disorder of the newborn with an incidence of $1/140000 \sim 1/250000$ [1, 2]. It often presents with angular deformities, cysts, and epiphyseal stenosis. They are prone to re-fracture after spontaneous or minor trauma, heal poorly with conventional treatment, and eventually develop pseudarthrosis [3, 4]. In order to maintain stability in pseudarthrosis, multiple operations are often required to achieve fracture healing [2, 3]. Although surgical approaches and early healing rates have been improved, there are still problems such as high refracture rates, limb shortening and angulation, which pose serious challenges to clinical management [5-7].

Studies have shown that children with CPT are usually associated with neurofibromatosis type 1 (NF1), a disorder in which there is a loss of function of the NF1 gene, and CPT is also a rare manifestation of NF1 [8, 9]. During skeletal development, the deletion of the NF1 gene decreases the level of bone metabolism, and children's bones exhibit excessive catabolic and anabolic deficiencies with a decreased level of 25-hydroxyvitamin D3 (25-OHD). NF1 patients are also shorter than expected, indicating a general decrease in skeletal growth [10, 11]. Researches show that children and adults with NF1 have lower bone mineral density and exhibit less intense bone metabolism than normal [10-12]. Previous study by our team has also found that exosomes derived from the serum of children with CPT associated with NF1 reduce bone formation [13]. However, to date, there have been few clinical studies on bone

metabolism levels in these patients, and it remains unclear whether bone metabolism in children with CPT differs from that of normal subjects.

Bone strength is the ability of bone's resistance to fracture for a given condition, bone stiffness index (STI) and bone mineral density estimation (BMDe) are important parameters for evaluating bone strength [14]. Quantitative ultrasound is the most effective and widely used method for assessing bone strength in children [15]. It is performed by measuring the tibia bone to obtain broadband ultrasound attenuation (BUA) and speed of sound (SOS) [15]. The quantitative ultrasound index (QUI), STI and BMDe can be calculated by these two parameters [16]. Compared with other BMDe testing methods, the quantitative ultrasound technique has the advantages of simplicity, convenience, no radiation, high accuracy, and low requirements for infant cooperation, so it is widely used for BMDe detection during the growth and development of children [15, 16].

As children with CPT are always associated with NF1 symptoms, and tibial pseudarthrosis is clinically difficult to cure. Therefore, we hypothesized that these conditions may be caused by abnormalities in systemic skeletal metabolism. In this study, we used ultrasound bone densitometry to measure bone strength in children with CPT versus children with none bone metabolic diseases to detect the bone metabolism in children with CPT.

Materials And Methods

A cross-sectional study design was used to compare bone strength in CPT children with NF1 and normal children without bone metabolic disease. The study was conducted at Hunan Children's Hospital, and institutional review board approval was obtained for this study. The guidelines of the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) were followed to report the cross-sectional study [17].

2.1. Participants

Thirty-seven children aged 3 to 10 years with a diagnosis of CPT who had not received any previous treatment and 40 children without metabolic bone disease were included in this study. Participants were excluded if they had any known bone disease, other chronic diseases, previous or current treatment that might affect bone metabolism (eg, celiac disease, thyroid disorder, systemic glucocorticoids), or if the child was unable to co-operate with the study protocol. All participants had provided informed consent from their parents.

2.2. Data collection

All data are collected by the same researcher (S.X.), ensuring that all measurements are taken in the same way. General information was collected, including name, age, sex, and body mass index (BMI). The ultrasonic bone densitometer (Pegasus Smart Medilink, French) was used to examine the bilateral calcaneus of the subjects. The probe was placed correctly and should be facing the heel to avoid errors in the measurement results. The measured data are automatically analyzed by the computer system. According to the measurement results, we can get the BUA, SOS values, and then referred to the methods to calculate the QUI, STI and BMDe values [18, 19]. To verify the reliability of the measurement, twenty subjects were randomly selected from the CPT and control groups and measured repeatedly by two authors (GY and SX) with an interval of 1 months to examine inter- and intra-rater agreements.

2.3. Observation index

Broadband ultrasound attenuation (BUA): ultrasound waves will be attenuated when passing through an elastic medium. During the measurement process, the transmitting probe of the bone densitometer emits ultrasound signals, which are received and amplified by the receiving probe after passing through the bone sample to obtain the corresponding transmitted signals. The transmitted signal is processed accordingly to obtain the attenuation curve. The attenuation is linearly related to the frequency. The slope of the attenuation curve is BUA. The thicker the bone, the greater the bone density, the greater the attenuation of the signal at the same frequency, and the greater the corresponding slope. The BUA value is related to the average density, size, spacing, orientation and scattering intensity of the bone trabeculae. Due to low bone calcium density, patients with osteoporosis have lower BUA values than normal individuals.

Speed of sound (SOS): the ultrasound emission time and signal reception time were recorded and the SOS value was obtained based on the width of the sample. It is an indicator to evaluate bone quantity and quality, bone condition and bone strength, and is proportional to bone volume.

Bone strength index (STI): according to the obtained results, $STI = 0.67 \times BUA + 0.28 \times SOS - 420$, which is an index obtained from the linear combination of BUA and SOS and mainly reflects the stiffness and rigidity of bone. It is a linear combination of BUA and SOS. Several studies have shown that it reflects both the mass and structural properties of cancellous bone. It has a better correlation and higher accuracy with bone mineral density. The index predicts the risk of osteoporotic fracture better than ultrasound velocity or attenuation parameters alone.

Quantitative ultrasound index (QUI): Statistical methods based on previous descriptions[18], $QUI = 0.41 \times (BUA + SOS) - 571$.

Bone mineral density estimation (BMDe) formula: Refer to Magkos' method[19] to convert BUA and SOS values into BMD values as follows: $BMDe = 0.0025926 \times (BUA + SOS) - 3.687$.

2.4. Statistical Analysis

All data were expressed as mean ± standard deviation and processed by STATA (version 13.0, Stata Corp LP, TX, USA). The intraclass correlation coefficient (ICC) was calculated to estimate intra- and inter-rater agreement. According to Landis' definition, an ICC of 0.6-0.8 was considered good agreement and greater than 0.8 was excellent agreement. Paired t-tests were used to determine within-group differences for various quantitative measures of quantitative ultrasound. For between-group analysis, t-tests were used to determine differences in various quantitative measures. Multivariate liner regression was used to investigate the relationship between differences in quantitative ultrasound measurements and age, BMI, NF1, and CPT Crawford type. P<0.05 was considered statistically significant.

Results

3.1.1. Baseline data and measurement reliability

In total, we reported 37 pairs of calcaneus scans from CPT patients and 40 pairs of scans from the controls. Among the CPT patients, 19 were Crawford type-II, and 18 were Crawford type-IV. The demographic characteristics of CPT patients and controls were shown in **Table 1**. Reliability evaluation had shown that all quantitative measurements had good to excellent intra- and interlocal agreement according to Landis' definition (**Table 2**).

Table 1 Baseline characteristics of CPT patients and controls.

	CPT Group (n=37)	Control Group (n=40)	P
Male	23	24	0.85
Female	14	16	
Mean Age (year)	3.14±1.81	3.32±2.66	0.32
BMI (kg/m ²)	15.47±3.0	15.74±3.75	0.53

Table 2 Reliability of quantitive ultrasound measurements.

Measurement	Intra-rater agreement		Inter-rater agreement	
	ICC	95% CI	ICC	95% CI
SOS	0.95	0.92,0.98	0.97	0.94,0.98
BUA	0.91	0.87,0.93	0.92	0.90,0.96
STI	0.96	0.92,0.98	0.95	0.93,0.96
QUI	0.97	0.93,0.98	0.92	0.91,0.94

ICC, intra-class correlation coefficient; 95% CI, 95% confidence interval.

3.2. Quantitive ultrasound measurements

The quantitive ultrasound measurements between CPT patients and controls were presented in Table 3. Overall, the CPT patients exhibited significantly lower SOS, STI, QUI and BMDe than the controls (Table 3). Whereas no significant difference was found in the BUA values between the CPT patients and controls (**Table 3**).

Table 3 Intragroup differences in the measurements of quantitive ultrasound.

Measurement	CPT Group (n=37)			Control Group (n=40)		
	Affected	Contralateral	P	Left	Right	P
SOS	1371.67±58.63	1365.85±185.70	0.85	1412.41±73.02	1419.64±59.2	0.52
BUA	43.01±6.57	45.04±8.84	0.18	46.1±11.5	47.85±13.08	0.31
STI	-7.08±17.03	-7.39±52.34	0.97	6.36±18.6	9.56±15.05	0.27
QUI	9.04±24.22	7.46±76.23	0.90	26.99±28.29	30.67±22.50	0.40
BMDe	-0.02±0.15	-0.03±0.48	0.90	0.09±0.18	0.12±0.14	0.40

For the above statistically significant parameters, we selected SOS, STI, QUI and BMDe as dependent variables and defined age, BMI, gender and NF-1 as independent variables. The final multiple linear regression model was not statistically significant and the regression coefficients of the measurements obtained by quantitative ultrasound with age, gender, BMI and NF-1 were not statistically significant (**Table 4**).

Table 4. Intergroup differences in the measurements of quantitive ultrasound

Measurement	CPT Group[n=74]	Control Group[n=80]	t	P
SOS	1368.75(±136.78)	1416.02(±66.15)	2.7617	0.0065*
BUA	44.0541(±7.7963)	46.975(±12.294)	1.7447	0.0831
STI	7.2319(±38.6525)	7.96(±16.884)	3.2013	0.0017*
QUI	8.2532(±56.1720)	28.8299(±25.461)	2.9643	0.0035*
BMD _e	-0.0241(±0.3552)	0.0180(±0.1610)	2.9643	0.0035*

We further analyzed the effects of age, sex, BMI, and Crawford classification of pseudarthrosis on SOS, STI, QUI, and BMD_e. The final regression model showed that STI was positively correlated with age. While SOS, STI, and QUI were all negatively correlated with gender and CPT Crawford classification (**Table 5**).

Table 5 Associations of CPT differences parameters with age, gender, BMI and Crawford classification

Measurement	Age		Gender		BMI		C-Type		C-Type	
	coef.	P	coef.	P	coef.	P	coef.	P	coef.	P
SOS	3.262	0.130	-32.517	0.009*	6.63	0.065	-42.682	0.013*	-91.495	0.000*
STI	1.312	0.027*	-9.84	0.004*	1.522	0.119	-11.196	0.016*	-28.473	0.000*
QUI	1.581	0.068	-13.781	0.006*	2.513	0.081	-17.037	0.013*	-39.262	0.000*
BMD _e	-0.005	0.745	0.0051	0.956	0.033	0.224	0.011	0.931	-0.122	0.304

Discussion

CPT is a rare disease in pediatric orthopaedics. Once a fracture of the tibia occurs, it rarely heals naturally and usually results in a persistent pseudarthrosis. The treatment of CPT remains a surgical challenge, and fracture healing is difficult regardless of the surgical approach chosen[20]. There are many factors for the decreased ability of fracture healing and increased the occurrence of refracture, but it remains unknown whether it is related to the skeletal metabolism of the whole body.

Recently, quantitative ultrasound has been introduced as a detection tool for orthopaedic diseases, and its application in pediatric patients is also expanding [21]. Previous research showed that the detection rate of abnormal bone mass was significantly higher than that of dual-energy X-ray detection method [18]. However, the dual-energy X-ray detection method has the disadvantages of radiation exposure and difficulty in portability, which makes its use obviously limited.

In this study, quantitative ultrasound is used to detect the bone mineral density parameters of CPT and non-bone metabolic disease children. Our results show that the incidence of osteopenia in CPT group is higher than that in the control group, and the SOS, STI, QUI, and BMD_e of CPT children are lower than those of non-bone metabolic disease children. SOS is an index to evaluate the bone quality and strength, which is proportional to bone mass and can better predict the risk of fracture [22]. Therefore, our results suggesting that the bone mass of children with CPT may be lower than the controls, and could be more prone to fracture. STI and QUI are skeletal quality indicators, which reflects the hardness and stiffness of bone [23]. Our results indicating that the bone strength and stiffness of children

with CPT may be lower than those of children with non-bone metabolic diseases. Although the BMDe values are not directly measured by ultrasonic bone densitometry, the BMDe values estimated by Magkos' method are statistically different between the two groups, suggesting that the bone mineral density of children with CPT may also be lower than that of children without bone metabolic diseases. The above results indicate that the bone strength of children with CPT may be lower than that of the same age people without bone metabolic diseases, and there is bone loss, which may lead to increased bone fragility and easy fracture, and may also be associated with the high occurrence of refracture.

Studies have found that NF1 affects systemic bone metabolism [24, 25], and different clinical manifestations of pseudarthrosis are related to the occurrence of refracture [24, 26, 27]. To investigate whether differences in bone strength are associated with clinical symptoms of pseudarthrosis and the presence or absence of NF-1, we performed multiple liner regression analyses of statistically significant quantitative ultrasound parameters with the presence or absence of NF-1 and CPT Crawford classification, respectively. Our study here shows that SOS, STI, QUI are negatively correlated with Crawford classification, suggesting that the higher level of CPT Crawford classification with a less bone mass and strength, thus could lead a higher risk of bone fracture. However, there was no significant correlation between NF1 and SOS, STI, QUI, demonstrating that the presence or absence of NF1 has no significant effect on bone strength in children with CPT.

There are some limitations in this study. The above results obtained by cross-sectional studies require long-term follow-up, and the sample size may be small. In addition, children with CPT suffer from immobilization and pain of the affected limb thus may lead their physical activity reduced, and the change of bone mineral density may also be related to this. Thus, in future studies, we should recruit more subjects and identify more parameters to reduce the effects of the above impact factors.

Conclusion

In conclusion, by recruiting CPT and non-bone metabolic children, we found that the incidence of osteopenia in CPT group was higher than that in the non-bone metabolic disease group, and SOS, STI, QUI and BMDe were lower than those in the non-bone metabolic disease group, and this phenomenon is not related to NF1 while related to CPT Crawford classification, suggests that a higher CPT Crawford classification with lower bone strength and higher risk of fracture.

Abbreviations

CPT: Congenital pseudarthrosis of the tibia

BUA: Broadband ultrasound attenuation

SOS: Speed of sound

STI: Bone strength index

BMDe: Bone mineral density estimation

NF1: Neurofibromatosis type 1

ICC: Intraclass correlation coefficient

BMI: Body mass index

CI Confidence interval

Declarations

Author Contributions: Conceptualization, G.Y. and H.M.; methodology, H.Y.; validation, S.X., G.Z. and Y.L.; formal analysis, G.Y.; investigation, G.Y.; resources, H.M.; data curation, G.Y.; writing—original draft preparation, G.Y.; writing—review and editing, G.Y. H.Y. and H.M.; supervision, H.M. and H.Y.; project administration, H.M.; funding acquisition, H.M. All authors have read and agreed to the published version of the manuscript.

Funding

This research was funded by major science and technology projects for collaborative prevention and control of birth defects in Hunan province, grant number 2019SK1010.

Ethics approval and consent to participate

The study was approved by the Institutional Review Board of Ethics Committee of Hunan Children's Hospital (protocol code 2019HY00541). Written informed consent has been obtained from the patients to publish this paper.

Data Availability Statement: Not applicable.

Acknowledgments: Not applicable.

Consent for publication: Not applicable.

Conflicts of Interest: The authors declare no conflict of interest.

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